REMARKS

Amendments to the claims.

Claims 22, 27, 32, 37, and 45-48 are currently amended. Claims 24, 28 and 29 are canceled. New claims 49-51 are added. After entry of this amendment, claims 22, 25-27, 30-33, 36-38 and 41-51 will remain pending.

Support for "at least 50% amino acid identity to SEQ ID NO: 14" can be found at page 36, lines 32-33, i.e. "Transcription factors that are homologous to the listed sequences should share at least 50%, or at least about 60%, … identity over the entire length of the polypeptide or the homolog".

These amendments are being made in response to the final Office action, and were not made previously for that reason. No new matter has been added.

Response to specific items in the Office action.

Items 6 and 7. Rejection under 35 USC 112, first paragraph, written description

Claims 22, 24-33, 36-38, 41-42, and 45-48 are rejected for allegedly failing to comply with the written description requirement. Applicants believe this rejection has been avoided by the present amendment of the claims. Aspects of the rejection not addressed by the amendments to the claims are respectfully traversed. The specific elements of the Office action are presented in bold face.

> **The conserved domain (claim 22) represents only 34% of instant SEQ 1D NO: 14. Applicants do not provide evidence that this "conserved domain" in association with an AT hook domain describes a transcription factor that "when over-expressed in a transgenic plant confers to the transgenic plant greater drought tolerance or greater biomass relative to a control plant". (page 4 of the Office action)**

Applicants respectfully disagree with this assessment. The claimed sequences all belong to the AT-hook transcription factor family, and have at least a conserved AT hook domain and the second conserved domain as described. It is well-known that conserved domains are art-recognized as important and distinct functional and structural units of a protein. "The independent evolutionary histories of domains found within the same protein lead to an assumption that the domain is the fundamental unit of protein structure and function" (Doerks 2002 *Genome Res.* 12, attached, page 47, column 1), and "Conserved protein domains are most useful when they can be used to make predictions of likely function" (*Id*, page 49, column 2), and "On the basis of reports in the literature and/or co-occurrence with previously identified domains, some functional features can be predicted for 78.6% of our newly identified set of 28 domain families. This represents an increase in the state of functional prediction for ~700 proteins (i.e., the total number of distinct proteins that are covered by novel domains with a putative

function" (page 53, column 2). See also the NCBI's Conserved Domain Database (presently at: /blast.ncbi.nlm.nih.gov/Blast.cgi) which teaches that: "Conserved domains are functional units within a protein that have been used as building blocks in molecular evolution and recombined in various arrangements to make proteins with different functions…*The data are then used for putative functional annotation of protein query sequences* based on matches to specific hits (illustrated example) or superfamilies, identification of proteins with similar domain architectures, and protein classification" (www.ncbi.nlm.nih.gov/sites/entrez?db=cdd, *emphasis* added).

Applicants have disclosed two conserved domains of SEQ ID NO: 14, i.e. the AT-hook motif (nine amino acids) and the second conserved domain that corresponds to amino acids106-201 of SEQ ID NO: 14 (ninety-six amino acids), these two domains constitute 40% of SEQ ID NO: 14. The AT-hook transcription factor family are well-characterized by the presence of a conserved DNA-binding peptide motif called the "AT hook" which has an invariant peptide core motif of Arg-Gly-Arg-Pro (i.e., R-G-R-P) flanked on either side by other conserved positively charged amino acid residues. These AT-hook proteins preferentially binds to the narrow minor groove of stretches of AT-rich sequence (Reeves and Beckerbauer, 2001, incorporated by reference at page 16, line 16 of the instant specification, a PDF version is attached to this paper), these family of proteins function as promoting gene activation where, by acting as a sort of molecular 'glue', they facilitate formation of sterospecific complexes called enhanceosomes on the promoter/enhancer regions of inducible genes as a consequence of both specific protein-DNA and protein-protein interactions (*Id*, abstract). Reeves also illustrated the organizations of the protein-coding exons of AT-hook proteins from human, mouse and plant (*Id*, Figure 1), and taught that the AT hook motifs are highly conserved cross these widely diverse species.

The second conserved domain, referred to as a domain with unknown function (page 27), comprises almost all of the art-recognized DUF296 domain by conserved domain analysis using methods provided at www.ncbi.nlm.nih.gov. Alves et al. 2009 (submitted to the Office with the previous response) also noted that DUF296 is a domain of unknown function that contains what appears to be a zinc finger like motif, which suggests that these proteins may be involved in DNA binding, probably acting in regulation of gene expression (the second paragraph at page 10 of Alves et al., 2009, *supra*). Richardt et al., 2007 (submitted to the Office with the previous response) also recognized that "PT007 might represent a novel TF family is fortified by the domain structure of the members, most of which contain the two PFAM domains AT hook (PF02178) … and DUF296 (PF03479), which are known to be present in this particular order in a class of proteins that is thought to have DNA-binding activity" (column 2, page 1459 of Richardt et al., 2007, *supra*). Richardt also cited Weigel et al., 2000 in which overexpression of a protein containing DUF296 has been shown to lead to late flowering and modified

leaf development in *Arabidopsis* (column 2, page 1459 of Richardt et al., 2007, *supra*).

Applicants note that Reeves stated "nevertheless, because of their unique combination of structural and biological characteristics, the HMGI/Y proteins are also involved in a diverse range of other cellular processes", however, the presently claimed AT-hook transcription factors have not only the unique structural combination of the AT-hook motif that is common to all AT-hook transcription factors, but also the second conserved domain and the high structural similarity to SEQ ID NO: 14, and these AT-hook transcription factors as claimed all have the function of conferring drought tolerance or greater biomass. The correlation between the claimed structures and the function are evident in view of the large number of representative functional sequence species with the claimed structure. The specification in page 26-27 has provided structure elements and their molecular function of AT hook motif-containing transcription factors. Applicants have provided at least seventeen examples such as G3456 (SEQ ID NO:14), G3401 (SEQ ID NO:38), G3460 (SEQ ID NO:18), G2153 (SEQ ID NO:6), G3459 (SEQ ID NO:16), G1069 (SEQ ID NO:42), G1076 (SEQ ID NO:54), G3556 (SEQ ID NO:40), G3399 (SEQ ID NO:10), G2157 (disclosed in Figure 12A, and also disclosed as SEQ ID NO: 448 in the priority US application No. 10/225,066), G3407 (SEQ ID NO:34), G1073 (SEQ ID NO:2), G3400 (SEQ ID NO:30), G1067 (SEQ ID NO:4), G2156 (SEQ ID NO:8), G1945 (SEQ ID NO:44), G3408 (SEQ ID NO:20); all of these sequences are highly homologous to SEQ ID NO: 14 (please see the sequence analysis in Exhibit A), and have the AT hook domain and the second conserved domain that are highly homologous to amino acids 62-70 and 106-201 of G3456 SEQ ID NO: 14, respectively (please see the summary in Table 1 of the previous response submitted to the Office on 22 July 2009). These sequences have been introduced into plants and found to have conferred greater drought tolerance or greater biomass compared to a control plant when overexpressed (Table 1, *Id*). Thus, contrary to the Office's assertion cited in bold as above, Applicants have provided a large body of evidence in the form of numerous representative working examples that this "conserved domain" in association with an AT hook domain and sufficient sequence homology to SEQ ID NO: 14 indeed describes a genus of transcription factors that "when over-expressed in a transgenic plant confers to the transgenic plant greater drought tolerance or greater biomass relative to a control plant"

Applicants respectfully remind the Examiner that the scope of claim 22 and its dependent claims are also further defined by being able to hybridize to G3456, SEQ ID NO: 13, under defined stringent conditions which are at least as stringent as 6x SSC at 65° C. Applicant notes that the USPTO's own "Synopsis of application of written description guidelines" provides, in "Example 9", a case in which a "specification discloses a single cDNA (SEQ ID NO: 1) which encodes a protein [with a defined function]" and "an example wherein the complement of SEQ ID NO: 1 was used under highly stringent

conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that [confer the same function]. The hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that [confer the same function]. And, "[t]he claimed invention is adequately described". This may be favorably contrasted with the present application, where a large number of sequences that are structurally similar and predicted to hybridize to SEQ ID NO: 13 under stringent conditions (please see the response submitted on 7/22/09), and Applicant have confirmed that all the sequences, except for one, e.g., G1076, SEQ ID NO; 54, which has not yet been fully tested in plants, have the claimed function.

Applicants note that the present claims recited an additional functional limitation of being able to confer greater drought tolerance or greater biomass to plants, which is correlated with the presence of the two conserved structural domains and sufficient structural similarity to SEQ ID NO: 14 as described above. Non-functional sequences can be excluded after testing for the claimed function using methods that are art-known and described (see Example VIII).

It is noted that written description can be satisfied by "disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics" (MPEP § 2163.II.A.3(a), citing to *Enzo Biochem., Inc. v. Gen-Probe, Inc.* 323 F.3d 956, 964; 63 USPQ2d 1609, 1613 (CAFC 2002)). As discussed above, Applicants have disclosed numerous representative sequences from diverse plant species, which have two conserved domains and are at least 50% identical to SEQ ID NO: 14. Applicants have additionally disclosed sufficient relevant identifying structure elements of the claimed genus, i.e. the AT hook motif and the second conserved domain that are highly homologous to those present in G3456, SEQ ID NO: 14, and also functional characteristics, i.e. conferring drought tolerance or greater biomass, coupled with a disclosed and art-recognized correlation between the structure and function. Therefore, one of ordinary skill in the art would recognize that Applicants were in possession of claimed invention at the time of filing.

The specification at pages 94-95 describes no structural and functional relatedness among these AT-hook transcription factors. (page 5, first paragraph of the Office action)

Applicants note that, although pages 94-95 do not specifically discuss the structural and functional relatedness of AT-hook transcription factors, there are sufficient disclosures throughout the application that have discussed the significant structural elements of AT-hook transcription factors and taught their relatedness to their function throughout the rest of the disclosure. For example, page 25, lines

31-33 shows that the AT-hook domain of the disclosed sequences of sufficient homology to the AT-hook domain of G1073 (SEQ ID NO: 2), which enables these polypeptides to bind the narrow minor groove of AT-rich regions of DNA and regulate transcription; Table 1 further provided the amino acid coordinates of the conserved AT-hook domains and the second conserved domain and compared the sequence identity with the canonical sequence G1073, SEQ ID NO: 2; Figure 5A-5C showed the sequence alignments of the many disclosed AT-hook transcription factor family and illustrated the identical or conserved residues among this group of proteins. Furthermore, the specification, taught the detailed structural features of G1073, which has 65% amino acid sequence identity in the second conserved domain to that of G3456, SEQ ID NO: 14, and the AT-hook domain that comprises a single AT-hook DNA binding motif (RRPRGRPAG), a highly conserved 129 amino acid residue domain with unknown function (corresponding to the claimed second conserved domain) (Table 1, and pages 27-28). Applicants disclosed that G1073 has a potential acidic domain spans from position 172 to 190, three potential protein kinase C phosphorylation sites at Ser32, Thr83 and Thr102, as indicated by the analysis of the protein using PROSITE, and three potential casein kinase II phosphorylation sites at Ser6, Ser70 and Ser247 (Figure 3). Figures 5A-5C described the G1073 protein contains a shorter N-terminus compared to many other AT-hook proteins.

Many of the disclosed functional sequences in the application, including G3456, SEQ ID NO: 14, are phylogenetically related to G1073, SEQ ID NO: 2. It is well known in the art that protein function can be classified using phylogenetic analysis, for example, with multiple alignments and/or phylogenetic trees, which allows one to identify structural and functional boundaries, thus establishing a basis for accurate predictions based on a specific, experimentally determined level of relatedness. The art also recognizes that functional predictions can be greatly improved by focusing on how the genes became similar in sequence (i.e., by evolutionary processes) rather than on the sequence similarity itself (page 163, col.1, Eisen, 1998, attached). In fact, many specific examples exist in which gene function has been shown to correlate well with gene phylogeny (page 165, col. 3, ¶2, Eisen, 1998). AT-hook transcription factors are well-known to have conserved domains that correlate with their function, (please see previous discussion at page 6 of this response). The claimed sequences belong to a specific group of AT-hook proteins, which are phylogenetically related (please see Figure 4) and have similar structure and function to SEQ ID NO: 14. This structure-function relatedness is even more evident when considering that having a conserved domain that is at least 65% identical to amino acids 106-201 of SEQ ID NO: 14 and being encoded by polynucleotide sequence that can hybridize to SEQ ID NO: 13, always co-exist with having the function of conferring greater drought tolerance and/or greater biomass relative to controls among the disclosed functional sequence species. One of skill in the art would readily recognize that the correlation

between the claimed structure and function goes much beyond the disclosed exemplar sequences as they are derived from diverse plant species including monocots and dicots, and they represent a practical sampling of the very large number of plant sequences that would also have the claimed structure and function.

Applicants' own arguments demonstrate that only the extremes of the claimed genus have been described, not a representative number of species that describe the variation within the genus. (page 5, second paragraph of the Office action)

Claims 22, 23, 32 and 37 are directed to sequences that are at least 50% identical to SEQ ID NO: 14 in amino acid sequence and have conserved domain of at least 65% identity to amino acids 106-201 of SEQ ID NO: 14, not whole protein identity. As we show in the previous response, the numerously listed examples have the amino acid sequence identity of 100%, 75%, 74%, 71% (two sequences), 69%, 68%, 66%, 65%, 64%, 63%, 61% (two sequences), 51%, and 47%, they represent a considerable amount of variations within the claimed genus, not just the extremes. Applicants note that there is no rigid requirement that a patent application must individually list multiple, particular species in order to meet the requirement for written description, rather, "[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A 'representative number of species' means that the species which are adequately described are representative of the entire genus" (please see MPEP 2163.05). The US patent office has established what constitutes a representative number when dealing with a genus of nucleotides: "[w]hen there is substantial variation within the genus, it may require a description of the various species which reflect the variation within the genus. For example, a broadly drawn claim to a specific gene from ruminant mammals may require a representative species from cattle, buffalo, bison, goat, deer, antelope, camel, giraffe and llama" (Request for Comments on Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 1 "Written Description" Requirement", 1212 OG 15, June 9, 1998). The disclosed sequences are derived from evolutionarily diverse plant species, including soy, rice and *Arabidopsis*, they represent a practical sampling of large number of sequences existed across the plant kingdom that have the similar structure, i.e. having at least 50% amino acid sequence identity to SEQ ID NO: 14, having a conserved domain that is at least 65% identical to amino acids 106-201 of SEQ ID NO: 14, and being encoded by polynucleotides that can hybridize to SEQ ID NO: 13 or its complement under stringent conditions, and similar function, i.e. conferring greater drought tolerance or greater biomass comparing to a control plant. For example, G3456 is derived from dicot plant soy, while G3401, is from monocot plant rice (75%), there are many dicot plant species that are closer to soy than rice in the evolutionary tree, which would be more likely to generate sequences that have structure and function similar to that of G3456. Furthermore,

based on the evident correlation between the conserved structures and function in AT hook transcription factors in general from prior art and among the claimed specific genus as evidenced by the many functional species disclosed in this application, one of ordinary skill in the art would recognize that sequences that have higher similarities in structure to SEQ ID NO: 14, especially in the two conserved domains, would even more likely to have similar function to SEQ ID: 14. From the teachings in the specification about how to introduce conserved substitutions while retaining the protein function, one of ordinary skill in the art would immediately appreciate that the sequences that have a conserved domain that is greater than 75% sequence identity to amino acids 106-201 could be readily generated and they will have the function of conferring greater drought tolerance or greater biomass relative to controls. Similarly, claims 45-48, which claim sequences that are at least 85% identical in amino acid sequence to SEQ ID NO: 14, are also fully supported even there is no actual sequence that have 85% is disclosed. In *Falkner v. Inglis*, the Federal Circuit has held that "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." (*Falkner v. Inglis* 79 USPQ2d 1001. (Fed. Circ. 2006). The court emphasized that a patent specification is written for a person of skill in the art, and such a person "comes to the patent with the knowledge of what has come before… it is unnecessary to spell out every detail of the invention in specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." (*Falkner, supra*, 1007). Here, as explained above, one of ordinary skill in the art comes to the application with all the knowledge regarding the structure-function relatedness of the AT hook transcription factors, the instant application disclosed that SEQ ID NO: 14 and many other sequences having less than 85% amino acid sequence identity (G3408, G1945, G1073 polypeptides have less than 50% amino acid sequence identity, please see Exhibit A) to SEQ ID NO: 14 have the claimed function, thus, one of skill would understand that sequences of higher structural similarities (over 50% or 85% identity in amino acid sequence) would also likely have the function of conferring greater drought tolerance or greater biomass as compared to control plants, and one would recognize that Applicants were in possession of the invention regarding the sequences that are at least 85% identical to SEQ ID NO: 14.

Furthermore, the facts here resemble those in Example 11B: ART-RECOGNIZED STRUCTURE FUNCTION CORRELATION PRESENT of the Written Description Training Materials Revision 1, March 25, 2008. In Example 11B, claim 2 relates to an isolated nucleic acid that encodes a polypeptide that has 85% identity to a reference sequence and, where the polypeptide has activity Y. The exemplar

specification of Example 11B provides only a single sequence species that encodes a polypeptide with the activity Y and discloses data that identify two domains as critical to the novel activity, i.e., a binding domain and a catalytic domain. The exemplary specification also proposes that conservative mutations in these domains will still result in a protein having said activity, whereas most non-conservative mutations in these domains will not result in a polypeptide having the recited activity. Nonetheless, "the disclosure of SEQ ID NO: 2 combined with the knowledge in the art regarding the genetic code would put one in possession of the genus of nucleic acids that encode SEQ ID NO: 2. Further, with the aid of a computer, one could list all of the nucleic acid sequences that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2". Additionally, the Office held that "the level of skill and knowledge in the art is such that one of ordinary skill would be able to use conventional sequencing and nucleic acid synthesis techniques to routinely generate and identify nucleic acids that encode the polypeptide of SEQ ID NO: 2, as well as those that encode any polypeptide having 85% structural identity to SEQ ID NO: 2". The Office thus held that claim 2 of Example 11B is properly supported by the description in the specification.

The instant claims 45-48 are narrower in scope than that of Example 11B, since they require additional structural limitations including having a conserved domain that is at least 65% identical amino acids 106-201 of SEQ ID NO: 14 besides having 85% amino acid identity to SEQ ID NO: 14, whereas the instant specification provides much better support than that of Example 11B in that it discloses numerous functional protein species from diverse plants, include, for example, sequences from rice, soy and *Arabidopsis* in addition to the two conserved domains, e.g., the AT hook motif and the second conserved domain. These exemplar sequences all have the claimed structures and conferred greater drought tolerance or greater biomass when overexpressed in plants. Applicants have discussed the structure-function correlation above. The instant application thus described two recognizable, predictable domains in the claimed sequence, and claims 85% sequence identity (as does Example 11B), and for which there was only one disclosed sequence species.

In Example 11B, the Office has taught that "[a]lthough all conservative amino acid substitutions in these domains will not necessarily result in a protein having activity Y, those of ordinary skill in the art would expect that many of these conservative substitutions would result in a protein having the required activity. Further, *amino acid substitutions outside of the two identified functional domains are unlikely to greatly affect activity Y.* Thus, a correlation exists between the function of the claimed protein and the structure of the disclosed binding and catalytic domains". Thus, one of ordinary skill in the art would recognize that variants that have 85% identity to the instant SEQ ID NO: 14, which can be generated through conserved mutation, especially outside the conserved regions, would also most likely result in

proteins having the claimed function as SEQ ID NO: 14.

Accordingly, Applicant respectfully requests that the rejection under 35 USC §112, first paragraph, for lack of written description, be withdrawn.

Item 8. Rejection under 35 USC 112, first paragraph, enablement

Applicants believe that the present rejection on claims 22 and 24-31 for allegedly lacking enablement has been avoided by the present amendment of the claims. Aspects of the rejection not addressed by the amendments to the claims are respectfully traversed. The specific elements of the Office action are presented in bold face.

> **Applicants provide limited guidance on how to make and use the claimed genus of recombinant constructs as broadly claimed. It is recognized in the instant art that AT-hook (a type of HMG protein) proteins appear to play a role in transcription regulation by acting as accessory factors which influence the association of transcription factors with chromatin and act as transcription factor cofactors (Aravind *et a/1998,* Nucleic Acids Research 26(19): 4413- 4421, page 4413, right column, 1st paragraph). The art teaches that AT-hook motifs seem to be auxiliary elements necessary for cooperation with other DNA-binding activities in the same or different proteins (Aravind *et a/1998,* page 4413, right column 2nd paragraph). Aravind *et a/1998* teaches that the AT-hook is a short stretch of sequence similarity which makes it difficult to detect in conventional searches and discern scores which are statistically significant (page 4414, left column, 2nd paragraph). Aravind *et a/1998* in Table 1 on pages 4415-4417 teach that AT-hook proteins have a wide variety of specific functions including enzymatic activity, positive and negative regulation functions, and chromatin structural functions. Hence, given the nature of the invention, the breadth of the claims and the amount of direction or guidance present, it would have required undue trial and error experimentation to make and use the invention as broadly claimed.**
> **(page 7 and 8, Office action)**

Applicants respectfully disagree with the Examiner's legal analysis. Note that in order to be enabling, a specification "must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'" (In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed.Cir.1993). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed.Cir.1984).

"The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))

The Examiner does not appear to question the ability of the skilled artisan to follow the protocols

in the specification, nor does the Examiner appear to question whether those protocols would have enabled one skilled in the art to obtain the claimed polypeptides. Even if one accepts the argument that it would have been iterative and time consuming to practice the invention, which Applicants dispute, undue experimentation implied by the Examiner has little to do with the quantity of experimentation; it is more a function of the amount of guidance provided. *PPG Indus. Inc. v. Guardian Indus. Corp.*, 75 F3d. 1558, 1564, 37 USPQ2d 1618, 1623 (Fed Cir. 1996). The instant specification has provided sufficient guidance regarding how to find or generate sequences that have the claimed the structures through sequence alignment using well-known methods in the art, or throught introducing conservative or similar mutations to SEQ ID NO: 14, especially outside the conserved domains. These sequences are expected to confer greater drought tolerance or greater biomass to plants as the presence of the claimed structure is highly correlated with the function of the sequences (discussed in the section addressing the written description rejection). The specification have additionally taught how to make expression constructs and transform them into plants and test for the function of conferring greater drought tolerance and greater biomass. Indeed, at least seventeen sequences from a wide array of plant species have been successfully isolated and proved that they have the claimed function (see the previous discussion), these sequences represent only a practical sampling of the large number of plant polypeptides that one of skill in the art could readily identify and make use of following the guidance of the application.

Applicants note that the claimed AT-hook transcription factors contain not only the AT-hook motif as the stated by the Office action, but also contain a second conserved domain that is at least 65% identical to 106-201 of SEQ ID NO: 14 and also have at least 50% amino acid sequence identity to SEQ ID NO: 14. The presence of the both motifs with the recited percent identity together with the ability to hybridize under stringent conditions to SEQ ID NO: 13 distinguish the claimed sequences from other AT-hook motif containing proteins. As discussed with the issue of the written description rejection, there are significant teachings in the art regarding the structural elements of the AT- hook transcription factors in relation to their activities to guide one skilled artisan to make variants of SEQ ID NO: 14 while retaining its function. For example, it has been shown in NMR and CD studies of a co-complex of individual AT hooks with a synthetic DNA substrate that the AT-hook peptide bound to the minor groove of a synthetic duplex with a central sequence of 5'-AAATTT-3', and the side chains of the arginine residues of the AT hook motif projecting into the minor groove and making hydrophobic contacts with adenine base (Reeves and Beckerbauer, 2001, page 16, 2nd column). It has been concluded that both the structure and position of the prolines of the AT-hook motif are crucial as studies showed that when the conserved prolines are either artificially mutated to alanine residues or when their position in the peptide motif is altered, the resulting mutant peptides will no longer preferentially bind to AT-rich sequences of DNA in vitro; and

proteins with specific mutations in these residues act as dominant negative competitors for HMGA [AT-hook proteins] function in vivo when introduced into mammalian cells (*Id*, page 17, 1st column). Even Aravind et al. (cited in the Office action) recognize that "the importance of this short conserved sequence (AT hook motif) is stressed by the observation that it is necessary and sufficient to bind DNA" (Aravind et al. 1998, page 4413, 2nd column, second paragraph).

AT-hook transcription factors have diverse functions, however, Applicants are not claiming all the AT-hook transcription factors here, rather, the claimed sequences all belong to a specific subgroup of AT-hook proteins that have the distinct structure features, i.e., they are encoded by polynucleotides that are highly similar to SEQ ID NO: 13 in that all of them are able to hybridize to SEQ ID NO: 13 under stringent conditions, and have the conserved domains that are highly homologous to that of SEQ ID NO: 14, and they all have similar functions.It is noted that Applicants are not required to reason why the invention works; an inclusion of a theory of how the invention works is not necessary to meet the enablement requirement. *Fromson v. Advance Offset Plate, Inc*. 720 F2d 1565, 1570, 219 USPQ 1137, 1140 (Fed Cir. 1983). The presently amended claims specifically recite the functional limitation of conferring greater drought tolerance or greater biomass relative to a control plant, the specification has also provided examples for testing these functions (please see Example VIII). Applicants disclosed that the AT-hook domains of the disclosed sequences that have sufficient homology to the AT-hook domain of G1073, SEQ ID NO: 2, provided the amino acid coordinates of the conserved AT-hook domains and the second conserved domain, and compared the sequence identity with the canonical sequence G1073, SEQ ID NO: 2, (Table 1). Figure 5A-5C showed the sequence alignments of the many disclosed AT-hook transcription factor family and illustrated the identical or conserved residues among this group of proteins. Numerous working examples have demonstrated that the presence of all these structural features is associated with the function of conferring greater drought tolerance or greater biomass, please see the previous response submitted to the Office on 22 July 2009. The specification provided guidance on how to make conservative mutations to the SEQ ID NO: 14 while maintaining its activity (pages 47-49), and how to introduce the sequences to plants and test for their abilities of conferring drought tolerance or increased biomass. At the time of filing, the skill in the art is high. It was routine in the art to generate mutants and test for their activity. Courts have noted that in fields where the art typically engages in experimentation, even complex experimentation is not necessarily undue. Please see, e.g., *In re Certain Limited-Charge Cell Culture Microcarriers* 221 USPQ 1165, 1174 (Int'l Trade commission1983), aff'd sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F. 2d 1104, 227 USPQ 428 (Fed. Cir. 1985). There is ample guidance both from the specification in combination with the prior art teachings and through working examples that clearly allow one of ordinary skill in the art to practice the claimed

invention without undue experimentation. Thus, the claimed invention is enabled.

Accordingly, Applicants respectfully request that the rejection under 35 USC §112, first paragraph, for lack of enablement, be withdrawn.

Item 8. Rejection under 35 USC §103, obviousness

Claims 22, 24, 26-29, 31-33, 37-38, 42 and 45-48 are rejected as allegedly being unpatentable over Lin, X (NCBI Accession No. AAF04888, publicly disclosed on 2 November 1999), in view of Sawa et al (1999, Genes & Development 13: 1079-1088). This rejection has been avoided in part by the present amendments and respectfully traversed in part for the reasons set forth below.

> **Lin teaches an AT hook transcription factor polypeptide, and polynucleotides encoding same, that comprises a conserved domain that is 80.2% identical to amino acids 106-201 of instant SEQ ID NO: 14. Lin teaches Applicants' SEQ ID NO: 6.**
> **Sawa et al teach making transgenic plant using a recombinant construct encoding an AT-hook transcription factor using a CaMV 35S promoter at page 1083.**
> **It would have been *prima face* obvious to one of ordinary skill in the art at the time of Applicants' invention to modify the teachings of Lin to make a transgenic plant transformed with a recombinant construct encoding the AT hook transcription factor using the teachings of Sawa *et al.* Given the teachings of Sawa *et al.*, one of ordinary skill in the art would have had a reasonable expectation of success.**
> **(Office action page 8 and 9)**

Applicants thank the Examiner for providing the Lin and Sawa reference. Applicants note that Lin's NCBI submission described AAF04999 as a "hypothetical protein" and provided "no additional details recorded". Without any real world utility, one of ordinary skill in the art would not have even considered making a recombinant construct and introducing this sequence into plant. The fact Sawa et al., 1999 used a construct of 35S:FIL to express a protein that contains a HMG-related domain in plants does not cure the deficiency of providing the motivation of making the claimed invention because Sawa disclosure do not concern AT-hook transcription factors and should not be associated with the Lin NCBI submission as a basis for an obvious rejection.

Applicants note that not all HMG proteins are AT-hook transcription factors: "there are three distinct classes of DNA-binding motifs found in the HMG proteins" and only "the third family of HMG proteins comprises the HMG-I(Y) group which bind to the minor groove of DNA via a conserved nine amino acid peptide called an AT-hook. " (page 4413, 2nd column, first paragraph of Aravind *et al* 1998). According to Sawa, the FIL protein corresponds to GenBank accession no. AF074948 (the legend of Figure 3, page 1081, Sawa et al., 1999), the amino acid sequence is shown as below:

MSMSSMSSPSSAVCSPDHFSPSDHLCYVQCNFCQTILAVNVPYTSLFKTVTVRCGCCTNLLSVNM
RSYVLPASNQLQLQLGPHSYFNPQDILEELRDAPSNMNMMMMNQHPTMNDIPSFMDLHQQHEIPK
APPVNRPPEKRQRVPSAYNRFIKEEIQRIKAGNPDISHREAFSAAAKNWAHFPHIHFGLVPDNQP

VKKTNMPQQEGEDNMVMKEGFYAPAAANVGVTPY

It is evident that this protein lacks the signature motif of AT-hook transcription factors (i.e. G-R-P flanked by positively charged residues), which is highly conserved during evolution as a DNA binding element and is found in various proteins and transcription factors in organisms ranging from bacteria to humans (Reeves and Beckerbauer, 2001).

The FIL protein taught by Sawa is not an AT-hook transcription factor protein, but rather, a unique HMG domain protein. Please see page 1084 of Sawa et al., 1999, the left column, underneath the title "Structure of the FIL protein", where Sawa disclosed that "compared with other HMG proteins in yeast, animals, and plants, the structure of the FIL protein is unique". In contrast to many animal and plant HMG proteins, which "have an acidic domain at the carboxyl terminus and often a basic domain at the amino terminus", "the FIL protein has a long stretch of amino acid residues at the amino terminus of the HMG domain but lacks prominent basic or acidic domains". Rather than relates to AT-hook family, FIL protein shows some homology to GATA1 family members and Dof family members (*supra*, 1084, right column). Thus, contrary to the Examiner's assertion, Sawa did not teach transgenic plants overexpressing an AT-hook transcription factor; a person of ordinary skill in the art would not have tried to combine Lin and Sawa to produce the claimed plants and constructs, nor would he have a reasonable expectation of success in doing so without the Applicants' own disclosure in hand. The Supreme Court has "warn [ed] against 'temptation to read into the prior art the teachings of the invention in issue' and instruct[ed] courts to 'guard against slipping into the use of hindsight.'" *KSR Int'l* v. *Teleflex Inc.,* 127 S.Ct 1742 (2007), quoting *Graham* v. *John Deere Co.,* 383 U.S. at 36.

The presently amended claims are now limited to the recombinant constructs, transgenic plants and methods to make such plants that over-express polypeptides that are closely related to SEQ ID NO: 14 (including SEQ ID NO: 6) and can confer more drought tolerance or increased biomass relative to control plants. The Supreme Court in KSR has emphasized its focus on obviousness of combinations of known components: "A patent composed of several elements is not proved obvious merely by demonstrating that each element was independently known in the art" and "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". (Id. at 1739), and "[w]hen a patent simply arranges old elements with each performing *the same function it had been known to perform*, and yields no more than one would expect from such an arrangement, the combination is obvious". Id. (quoting *Sakraida v. AG Pro, Inc.* 425 U.S. 273, 282 (1976), *emphasis* added). It has been established that when considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." Recombinant constructs, plant cells or

plants transformed with the polynucleotide of SEQ ID NO: 6 have never existed before the claimed invention. Neither Lin's NCBI submission nor Sawa's publication has predicted the instant results, or teaches a "function it had been known to perform", i.e. conferring increased biomass or more drought tolerance by overexpressing SEQ ID NO: 6 in plants. Thus, the skilled artisan would have been unable to predict the function of SEQ ID NO: 6, and the instant improvement is much more than the "predictable use of prior art elements" and it is not obvious to one of ordinary skill in the art to make a recombinant construct comprising a polynucleotide encoding SEQ ID NO: 6, and/or transform a plant cell with the construct, then test the plant for a useful function in view of Lin NCBI submission and the Sawa reference.

Instant claims 45-48 have been included in this rejection based on Applicants' assertion that G2153 (instant SEQ 10 NO: 6) is 66.5% identical to SEQ 10 NO: 14 at page 15, last two lines of the Remarks filed 22 July 2009. This rejection is made because the Office's search shows Applicants' SEQ 10 NO: 6 to be 56.2% identical to Applicants' SEQ 10 NO: 14 as shown in the Office action attachment.

Claims 45-48 have been amended to recite the structural limitation of being at least 85% identical in amino acid sequence to SEQ ID NO: 14 to avoid this rejection.

Instant claims 32 and 33 are deemed obvious because the recited method steps would have been considered obvious; growing a transgenic plant cell in to a transgenic plant is obvious in view of the teachings of Sawa *et al.*
(Office action page 9)

In response, Applicant note that the test under 103 is whether in view of the prior art the invention as a whole would have been obvious at the time it was made. Interpreting invention as a whole requires consideration of all claim limitations. Claims 32 and 33 recite a step of providing a recombinant construct comprising polynucleotides that are highly similar in structure to SEQ ID NO: 14, i.e., a recombinant construct comprising a polynucleotide that hybridizes to a nucleic acid sequence comprising SEQ ID NO: 13 or the complement thereof under stringent conditions as claimed, and encoding an AT-hook transcription, and also a step of growing the transformed plant cell into a transgenic plant that over-expresses AT-hook transcription factor polypeptide encoded by said polynucleotide. Neither the references alone or in combination teach or suggested that over-expression of the claimed sequences in plants will result in greater biomass or greater drought tolerance. Both the recombinant constructs and the transgenic plants are unobvious in view of the cited prior arts as discussed above, and they constitute material limitations to the claimed methods; the claimed method steps could not be completed without the novel constructs and transgenic plants. Therefore, claims 32 and 33 are also unobvious in view of Lin and Sawa.

Accordingly, Applicants respectfully request that the rejection under 35 USC §103, be withdrawn.

CONCLUSION

Applicants believe that no additional fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Mendel Biotechnology, Inc. Deposit Account No. **50-1025.**

Respectfully submitted,
MENDEL BIOTECHNOLOGY, INC.

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Attachments: Doerks 2002
Reeves and Beckerbauer, 2001
Eisen 1998